

## Articles



# Surgical excision versus imiquimod 5% cream for nodular and superficial basal-cell carcinoma (SINS): a multicentre, non-inferiority, randomised controlled trial

Fiona Bath-Hextall, Mara Ozolins, Sarah J Armstrong, Graham B Colver, William Perkins, Paul S J Miller, Hywel C Williams, on behalf of the Surgery versus Imiquimod for Nodular and Superficial basal cell carcinoma (SINS) study group\*

## Summary

**Background** Basal-cell carcinoma is the most common form of skin cancer and its incidence is increasing worldwide. We aimed to assess the effectiveness of imiquimod cream versus surgical excision in patients with low-risk basal-cell carcinoma.

**Methods** We did a multicentre, parallel-group, pragmatic, non-inferiority, randomised controlled trial at 12 centres in the UK, in which patients were recruited between June 19, 2003, and Feb 22, 2007, with 3 year follow-up from June 26, 2006, to May 26, 2010. Participants of any age were eligible if they had histologically confirmed primary nodular or superficial basal-cell carcinoma at low-risk sites. We excluded patients with morphoeic or recurrent basal-cell carcinoma and those with Gorlin syndrome. Participants were randomly assigned (1:1) via computer-generated blocked randomisation, stratified by centre and tumour type, to receive either imiquimod 5% cream once daily for 6 weeks (superficial) or 12 weeks (nodular), or surgical excision with a 4 mm margin. The randomisation sequence was concealed from study investigators. Because of the nature of the interventions, masking of participants was not possible and masking of outcome assessors was only partly possible. The trial statistician was masked to allocation until all analyses had been done. The primary outcome was the proportion of participants with clinical success, defined as absence of initial treatment failure or signs of recurrence at 3 years from start of treatment. We used a prespecified non-inferiority margin of a relative risk (RR) of 0.87. Analysis was by a modified intention-to-treat population and per protocol. This study is registered as an International Standard Randomised Controlled Trial (ISRCTN48755084), and with ClinicalTrials.gov, number NCT00066872.

**Findings** 501 participants were randomly assigned to the imiquimod group (n=254) or the surgical excision group (n=247). At year 3, 401 (80%) patients were included in the modified intention-to-treat group. At 3 years, 178 (84%) of 213 participants in the imiquimod group were treated successfully compared with 185 (98%) of 188 participants in the surgery group (RR 0.84, 98% CI 0.78–0.91; p<0.0001). No clear difference was noted between groups in patient-assessed cosmetic outcomes. The most common adverse events were itching (211 patients in the imiquimod group vs 129 in the surgery group) and weeping (160 vs 81). We recorded serious adverse events in 99 (40%) of 249 participants in the imiquimod group and 97 (42%) of 229 in the surgery group had serious adverse events, but none were regarded as related to treatment. 12 (5%) participants in the imiquimod group withdrew because of adverse events compared with four (2%) in the surgery group.

**Interpretation** Imiquimod was inferior to surgery according to our predefined non-inferiority criterion. Although excisional surgery remains the best treatment for low-risk basal-cell carcinoma, imiquimod cream might still be a useful treatment option for small low-risk superficial or nodular basal-cell carcinoma dependent on factors such as patient preference, size and site of the lesion, and whether the patient has more than one lesion.

**Funding** Cancer Research UK.

## Introduction

Basal-cell carcinomas make up 80% of all skin cancers and are the most common malignant disease in white populations. The incidence of basal-cell carcinoma is increasing worldwide by up to 10% per year,<sup>1</sup> and is also increasing in young people.<sup>2–4</sup> Skin cancer is a growing health problem and puts a substantial burden on the resources of health-care systems.<sup>5,6</sup> Although various treatment options are available for patients with low-risk basal-cell carcinoma, surgery is regarded as the gold standard.<sup>7</sup> Surgical treatment is largely done by

dermatologists and plastic surgeons, although treatment of low-risk disease can be undertaken by other health-care professionals with additional skills in skin cancer—eg, by family doctors or by professionals at local community hospital or treatment centres.<sup>8</sup>

Studies identified in our previous systematic review<sup>7</sup> have reported successful treatment with imiquimod cream; with 87–88% of patients with superficial basal-cell carcinoma, using a once-daily regimen for 6 weeks being successfully treated, and 76% of patients with nodular disease following once-daily treatment for

*Lancet Oncol* 2014; 15: 96–105

Published Online

December 11, 2013

[http://dx.doi.org/10.1016/S1473-2045\(13\)70530-8](http://dx.doi.org/10.1016/S1473-2045(13)70530-8)

See [Comment](#) page 12

\*See appendix for full list of study investigators

Centre for Evidence Based

Dermatology

(F Bath-Hextall PhD,

M Ozolins MSc,

Prof H C Williams DSc) and

School of Nursing, Midwifery,

and Physiotherapy

(F Bath-Hextall) and National

Institute of Health Research

(NIHR) Research Design Service

East Midlands

(S J Armstrong PhD), School of

Medicine (P S J Miller PhD),

University of Nottingham,

Nottingham, UK; Department

of Dermatology, Chesterfield

Royal Hospital NHS Foundation

Trust, Chesterfield, UK

(G B Colver DM); and

Department of Dermatology,

Nottingham University

Hospitals NHS Trust,

Nottingham, UK

(W Perkins FRCP)

Correspondence to:

Prof Hywel C Williams, Centre for

Evidence Based Dermatology,

University of Nottingham,

Nottingham NG7 2NR, UK

[hywel.williams@nottingham.ac.uk](mailto:hywel.williams@nottingham.ac.uk)

ac.uk

See Online for appendix

12 weeks.<sup>7,9</sup> However, none of these studies compared imiquimod with surgery. Imiquimod is an immune-response enhancer that probably works by activating toll-like receptor-7. The medicine is licensed in a cream form to be applied by patients for the treatment of external genital warts, superficial basal-cell carcinoma, and actinic keratoses in adults.<sup>10–12</sup> We postulated that topical imiquimod, although inferior to surgery, could still be an acceptable alternative because it might result in a better cosmetic appearance, especially for patients with low-risk basal-cell carcinomas of the face and neck, and because of the convenience of home application, plus possible cost and service savings. In this randomised study, we assessed whether imiquimod cream was non-inferior to surgical excision for treatment of low-risk basal-cell carcinoma.

## Methods

### Study design and patients

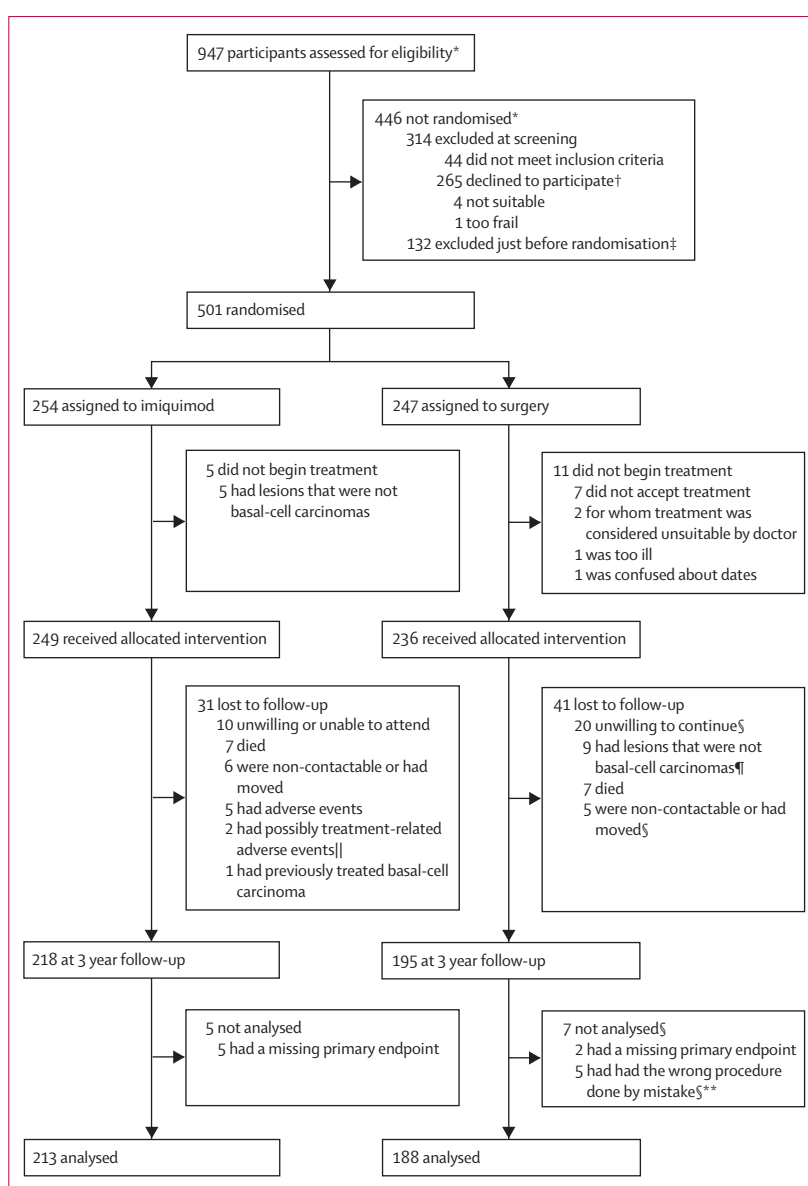
We undertook this multicentre, parallel-group, pragmatic, randomised, non-inferiority trial, in which patients were recruited between June 19, 2003, and Feb 22, 2007, with 3 year follow-up in clinic from June 26, 2006, to May 26, 2010, and longer follow-up from patients' notes from the last trial visit until up to 5 years and 4 weeks after the start of treatment. Participants were initially recruited from three dermatology secondary-care centres in the UK; from 2004 to 2006 an additional nine centres were added. The appendix has details of the study centres and participant recruitment. The study protocol has been previously published.<sup>13</sup>

Eligible participants of any age had histologically confirmed, primary, previously untreated, nodular or superficial basal-cell carcinoma not arising at sites at high risk for subclinical tumour spread, including the nose, ear, eyelid, eyebrow, and temple.<sup>14</sup> We excluded patients with morphoeic or recurrent basal-cell carcinoma and those with Gorlin syndrome.

The study had full ethics approval from the Nottingham Research Ethics Committee 2; all other sites had ethics approval. All participants gave written informed consent.

### Randomisation and masking

Participants were randomly assigned (1:1) via computer-generated blocked randomisation to receive topical imiquimod 5% cream or surgical excision with a 4 mm margin. The allocation sequence was prepared by the Trent Research and Development Support Unit (RDSU; Nottingham, UK) and randomisation was stratified by centre and type of basal-cell carcinoma. The research nurse was required to telephone Trent RDSU to obtain the allocated treatment for the next participant, which concealed the randomisation sequence from investigators. The Trent RDSU recorded the name of the next participant to be recruited and logged the date of the telephone call against the participant's identification number before specifying



**Figure: Trial profile**

\*Numbers who saw the nurse were not available from some smaller centres; an unknown greater number saw a doctor in clinic before assessment; potential participants were directed to the nurse who explained the study.

†Non-acceptance by eligible patients. ‡Because of unsuitable histology, death, poor health, regression of basal-cell carcinoma, participant was no longer available for follow-up or was unable to reach. §Excluded from safety analysis. ¶Not known before treatment. ||Both not serious. \*\*Electrodesiccation and curettage.

the treatment to which the participant was randomised. The research nurse arranged for the allocated treatment to be started and completed the case report forms. All allocated identification numbers were included in the database.

Because of the nature of the interventions, masking of participants was not possible. Masking of outcome assessors was only partly possible because surgery left a visible scar. The trial statistician was masked to allocation until all analyses had been done.

	Imiquimod (n=247*)	Surgery (n=220*)
Age (years)	69 (61–76)	67 (59–74)
Sex		
Men	145 (59%)	133 (61%)
Women	102 (41%)	87 (40%)
Fitzpatrick skin type†		
I	34 (14%)	29 (13%)
II	92 (37%)	101 (46%)
III	104 (42%)	78 (35%)
IV	15 (6%)	12 (6%)
Not recorded	2 (<1%)	0
Diameter (mm)	12 (9–16)	10 (8–15)
Site of lesion		
Face	91 (37%)	72 (33%)
Neck	15 (6%)	20 (9%)
Trunk	95 (38%)	86 (39%)
Arm	16 (6%)	16 (7%)
Leg	24 (10%)	20 (9%)
Other	7 (3%)	6 (3%)
Not recorded	0	0
Immunocompromised‡		
At baseline		
Yes	12 (5%)	7 (3%)
No	228 (92%)	205 (94%)
Unknown	5 (2%)	1 (<1%)
Not recorded	2 (<1%)	6 (3%)
During study		
Yes	3 (1%)	0
Previous basal-cell carcinoma		
Yes	82 (33%)	79 (36%)
Number of previous basal-cell carcinomas		
>3	19 (8%)	24 (11%)
1–3	63 (26%)	55 (25%)
0	165 (67%)	141 (64%)
Other skin cancers		
Yes§	18 (7%)	14 (6%)
No	228 (92%)	206 (94%)
Not recorded	1 (<1%)	0

Data are median (IQR) or n (%), unless otherwise indicated. \*Full dataset numbers (ie, modified intention-to-treat populations). †I=pale skin, burns very easily and rarely tans; II=fair skin that usually burns, but can gradually tan; III=sun that burns with long or intense exposure to the sun, but generally tans quite easily; IV=olive-coloured skin that always tans easily, but could possibly burn with lengthy exposures to intense sunshine; V=naturally brown skin, with brown eyes and dark hair; skin darkens easily with sun exposure and only burns with excessive exposure to the sun; VI=black skin with dark brown eyes and black hair; skin very easily darkens further on exposure to sun and would very rarely, if ever, burn. ‡Patients who were taking immunosuppressive drugs such as oral steroids, methotrexate, ciclosporin for suppression of immunological disorders, or to prevent transplant rejection. §Three (1%) patients with other skin cancers in the imiquimod group, and seven (3%) with other cancers in the surgery group had a previous history of invasive melanoma.

**Table 1: Baseline and demographic characteristics**

## Procedures

Treatment duration and frequency of dosing for imiquimod 5% cream were based on results from previous studies.<sup>15</sup> After the start of this study, imiquimod was licensed for treatment of superficial basal-cell carcinoma, with a 5 days per week dosing regimen.

Patients with superficial basal-cell carcinoma were instructed to apply the cream once daily for a total of 6 weeks. For patients with nodular disease, total application time was for 12 weeks.

Participants received an instruction sheet for how to apply the cream (separate sheets for nodular and superficial tumours). They were instructed to apply a thin layer to the lesion and to the 1 cm surrounding area before going to bed at night. The lesion was not to be covered (unless needed because of weeping or bleeding). Participants were asked to wash their hands after applying the cream, and to wash the cream off from the treatment site in the morning. Dosing was once daily because the study started before the manufacturers had decided on the final dosing regimen for basal-cell carcinoma. If a participant could not tolerate the cream because of side-effects, they were advised to stop treatment for a week and then restart at a frequency of 5 days a week. If this schedule was tolerated, the participant could go back to 7 days a week; if not, or if 7 days a week was not tolerated, a second time, they could go back to 5 days a week after a further rest period of 1 week. Treatment compliance was assessed for imiquimod by use of a daily diary and sachet returns. Patients who underwent surgery had simple excisional surgery with 4 mm margins (margins not checked). Dermatology consultants and dermatology trainees did surgery in line with usual local hospital arrangements to indicate the pragmatic nature of the trial. Compliance for surgery was confirmed by documentation of the date of surgery and whether or not a scar was visible at the next assessment.

The primary outcome was the proportion of participants with evidence of clinical success after 3 years from start of treatment. Clinically successful treatment was defined as no initial treatment failure or signs of subsequent local recurrence as reviewed by consultant dermatologists. We chose the 3 year timepoint for the primary endpoint because it was the last planned face-to-face visit that would enable measurement of clinical response in a way that would match clinical practice, and because 67% of recurrences of basal-cell carcinoma happen within the first 3 years after treatment.<sup>16</sup>

Secondary outcomes were clinical success at years 1, 2, and 5 (5 year data are not yet available); time to first failure (as stratified into within 1 year, between 1–2 years, and between 2–3 years); cosmetic appearance of lesion site as rated by the participant and dermatologist assessor; pain during treatment and in the 16 weeks of follow-up; the number of days the participant had moderate or severe pain during treatment and in the 16 week follow-up; and cost-effectiveness of imiquimod versus surgery.

## Statistical analysis

The original sample size for non-inferiority was based on a prestudy survey of UK dermatologists (unpublished data), which suggested that imiquimod needed to have roughly a 90% minimum chance of clinical success to

change practice, compared with a success rate of 97% for surgery. With a lower 98% confidence boundary of 84% (80% power, one-sided  $\alpha=1\%$ ), giving a total sample size of 740. Because of recruitment difficulties, we revisited the sample size calculation in March, 2006. Protocol amendment was approved by the research ethics committee and the data monitoring committee. We explored how the lower boundary of the CI varied for a range of sample sizes whereas all other assumptions used in the original calculation of sample size remained the same. This calculation showed that with a total sample size of 500, the lower limit of the confidence boundary of the imiquimod response rate would be 83%, and the additional gain in power from increasing the sample size to 550 and then to 600 was small. The precision of the response rate estimate for imiquimod would be within 10 percentage points of the actual imiquimod success rate for a sample size of 500, which was deemed acceptable to change practice. The non-inferiority margin based on these figures is a relative risk of 0.87 (lower boundary of a 98% CI for the relative difference in effect expressed as a relative risk), and only applies to the primary outcome. The sample size and choice of non-inferiority margin are fully reported in the study protocol.<sup>13</sup>

All analyses were done according to the protocol-specified statistical analysis plan, apart from the cost-effectiveness analysis, which we did with a different method to that originally planned because the first method was no longer appropriate. We applied *t*-tests, instead of bootstrap techniques and cost-effectiveness acceptability curves, to efficacy and cost data (appendix). We analysed data with Stata (version 10.1).

We recorded the characteristics of participants at baseline and summarised them for each treatment group with descriptive statistics. We did a modified intention-to-treat analysis on the full dataset, defined as all randomised participants with a histologically confirmed basal-cell carcinoma lesion who met the inclusion criteria and received at least one application of imiquimod cream or surgery, and for whom the outcome being analysed was available. We also did a per-protocol analysis for the primary outcome. This analysis started with the modified intention-to-treat population, with additional exclusion of patients who did not comply with the protocol procedures: those who received insufficient imiquimod (less than two-thirds of required dosing), those who had surgery by mistake after imiquimod, those who had additional surgery for early failure, and those who had complete curettage plus cryosurgery instead of biopsy for presumed treatment failure (histology negative).

We did sensitivity analyses for missing data for two measures: (1) the primary outcome measure (assuming the worst-case scenario of all participants with missing data having recurrence or treatment failure and the best-case scenario of all participants with missing data having been successfully treated); and (2) time to failure

(assuming the worst-case scenario with missing data replaced with the earliest time and the best-case scenario with missing data replaced with the latest time). We adjusted all analyses for centre, type of basal-cell carcinoma (superficial or nodular), size and site of tumour, and immunosuppression at baseline. In subgroup analyses for the primary outcome we assessed whether the intervention effect varied by tumour type (superficial *vs* nodular), tumour site (head and neck *vs* other sites), and tumour size ( $\leq 15$  mm *vs*  $>15$  mm diameters), by incorporation of an interaction term between treatment group and the covariate of interest in the regression models.<sup>17</sup>

For the primary outcome, we calculated the number and proportion of participants successfully treated at 3 years in each group, and the absolute difference in percentages between groups together with corresponding 98% CIs. We used Poisson regression with a robust error variance to estimate the treatment effect as a relative risk.<sup>18</sup> We analysed secondary outcome measures with the same method as that for the primary outcome variable. We rated the cosmetic outcome as excellent, good, fair, poor, very poor, and unable to see lesion, and we classed evaluable lesions as a success if they had an excellent or good appearance. We assessed pain daily on a scale consisting of no pain, and mild, mild to moderate, moderate, moderate to severe, and severe pain; we took pain during treatment to mean at least moderate pain on any one of the days during treatment. Time to failure

	Successfully treated with imiquimod	Successfully treated with surgery	Difference (%, 98% CI)*	RR (98% CI)†‡	p value§
<b>Modified intention-to-treat analysis</b>					
3 years					
Superficial	97/114 (85.1%)	96/98 (98.0%)	12.9% (4.4–21.3)	..	..
Nodular	81/99 (81.8%)	89/90 (98.9%)	17.1% (7.7–26.4)	..	..
All	178/213 (83.6%)	185/188 (98.4%)	14.8% (8.6–21.1)	0.84 (0.78–0.91)	<0.0001
2 years					
Superficial	101/116 (87.1%)	99/100 (99.0%)	11.9% (4.3–19.5)	..	..
Nodular	90/107 (84.1%)	92/93 (98.9%)	14.8% (6.2–23.4)	..	..
All	191/223 (85.7%)	191/193 (99.0%)	13.3% (7.6–19.3)	0.86 (0.80–0.92)	<0.0001
1 year					
Superficial	106/119 (89.1%)	99/100 (99.0%)	9.9% (2.9–17.0)	..	..
Nodular	95/111 (85.6%)	98/99 (99.0%)	13.4% (5.3–21.5)	..	..
All	201/230 (87.4%)	197/199 (99.0%)	11.6% (6.3–17.0)	0.88 (0.82–0.93)	<0.0001
<b>Per-protocol analysis</b>					
3 years					
Superficial	92/109 (84.4%)	96/98 (98.0%)	13.6% (4.8–22.3)	..	..
Nodular	76/93 (81.7%)	88/89 (98.9%)	17.2% (7.5–26.8)	..	..
All	168/202 (83.2%)	184/187 (98.4%)	15.2% (8.7–21.7)	0.83 (0.77–0.90)	<0.0001

Data are n/N (%), unless otherwise indicated. RR=relative risk. \*Surgery–imiquimod. †Imiquimod relative to surgery.

‡Relative-risk analysis covariates: centre, tumour type (nodular or superficial), tumour size, tumour site, and immunosuppression. §From likelihood ratio test.

**Table 2: Success at years 1, 2, and 3 in the modified intention-to-treat analysis and at year 3 in the per-protocol analysis**

	Imiquimod				Surgery				HR (98% CI); p value*
	Before 1 year	1–2 years	2–3 years	Number who did not fail	Before 1 year	1–2 years	2–3 years	Number who did not fail	
Superficial	13/114 (11%)	2/114 (2%)	2/114 (2%)	97/114 (85%)	1/98 (1%)	0/98	1/98 (1%)	96/98 (98%)	..
Nodular†	16/98 (16%)	0/98	1/98 (1%)	81/98 (83%)	1/90 (1%)	0/90	0/90	89/90 (99%)	..
All	29/212 (14%)	2/212 (<1%)	3/212 (1%)	178/212 (84%)	2/188 (1%)	0/188	1/188 (<1%)	185/188 (98%)	0·08 (0·02–0·32); p<0·001

All models adjusted for centre, tumour type, tumour site, and immunosuppression \*HR from continuation ratio model. †One less participant because the time category of failure was unknown for that participant; this individual is included in the sensitivity analyses.

**Table 3: Patients who failed treatment as stratified by timepoints, by type of basal-cell carcinoma and treatment group (modified intention-to-treat analysis)**

(one of five between-assessment time intervals) was analysed with a continuation ratio model with a complementary log-log link to estimate hazard ratios (HRs), and we used descriptive statistics to summarise the pain outcomes. Details of the methods of analysis are reported in the study protocol.<sup>13</sup> The appendix provides details of the cost-effectiveness analysis.

This trial is registered as an International Standard Randomised Controlled Trial (ISRCTN48755084), and with ClinicalTrials.gov, number NCT00066872.

#### Role of the funding source

The sponsors of the study and the company who donated the imiquimod had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit it for publication.

#### Results

The figure shows the trial profile. 501 participants were assigned to the imiquimod group (n=254) or the surgical excision group (n=247). 257 (51%) patients had superficial basal-cell carcinoma and 244 (49%) had nodular tumours as judged clinically on study entry. The appendix shows histology data. Five (2%) participants did not receive the intervention in the imiquimod group and 18 (7%) did not receive the intervention in the surgery group (figure 1). Seven (39%) of these 18 participants in the surgery group had a different surgical procedure done by mistake: two of these were lost to follow-up, but the remaining five were followed up to year 3 and excluded from the modified intention-to-treat analysis (figure 1). Five (31%) of these 16 patients in the surgery group had a different surgical procedure done by mistake but were followed up to year 3 and excluded from the modified intention-to-treat analysis (figure 1). 31 (12%) participants in the imiquimod group and 41 (17%) in the surgery group were lost to follow-up; five (2%) further participants in the imiquimod group and two (<1%) in the surgery group had a missing end point, leaving 401 (80%) patients for the modified intention-to-treat analysis at year 3 (figure 1).

Baseline characteristics were similar between the two groups (table 1). Median age of the participants was 68 years (range 30–92) and more men than women were

enrolled (table 1). Two-thirds of participants did not previously have basal-cell carcinoma (table 1).

At 3 years in the modified intention-to-treat population of 213 patients in the imiquimod group, and 188 patients in the surgery group, significantly fewer participants were successfully treated in the imiquimod group than in the surgery group (table 2). The lower limit of the 98% CI for successful treatment at 3 years (0·78) was less than the prespecified non-inferiority margin (0·87), and the upper limit was less than 1·0 (table 2); therefore, imiquimod was inferior to surgery. Similar results were shown in the per-protocol analysis of 202 patients in the imiquimod group and 187 patients in the surgery group (table 2) and results were unchanged in sensitivity analyses for missing data (data not shown).

The type of basal-cell carcinoma did not affect the difference in outcome between those treated with imiquimod and surgery. Fewer patients with superficial or nodular tumours were successfully treated in the imiquimod group than in the surgery group (table 2). We noted no significant interactions between treatment effect and tumour type, site, and size (data not shown). Our planned subgroup analysis showed clinical response rates of 92% (138/150 patients) for superficial lesions of 15 mm or less versus 89% (55/62) for lesions of more than 15 mm. Corresponding values for nodular lesions were 90% (138/153) and 89% (32/36), respectively. These results are pooled (surgery and imiquimod), but the models fitted in the multivariate analysis adjusted for treatment type and centre. After 1 and 2 years of follow-up, fewer patients, for whom the outcome data were available, were successfully treated in the imiquimod group than in the surgery group (table 2).

In the 3-year modified intention-to-treat population, significantly more tumours recurred or did not go away in patients in the imiquimod group in the first year of follow-up from start of treatment than in those in the surgery group (table 3). This finding was maintained for years 1–2 and years 2–3 of follow-up (table 3) in the same patient population. Participants in the imiquimod group had a shorter time to failure than did those in the surgery group (HR 0·08, 98% CI 0·02–0·32, table 3).

Data for participant-rated cosmetic appearance (at all sites) did not differ significantly between groups at 6 months and 3 years (appendix). Data were available for



	Imiquimod	Surgery	Difference (%; 98% CI)*	Relative risk (98% CI)†	p value‡
<b>6 months</b>					
Superficial					
Head and neck	17/30 (56.7%)	4/25 (16.0%)	-40.7% (-67.8 to -13.6)	..	..
All sites	33/112 (29.5%)	10/99 (10.1%)	-19.4% (-31.6 to -7.1)	..	..
Nodular					
Head and neck	35/63 (55.6%)	18/56 (32.1%)	-23.4% (-44.0 to -2.8)	..	..
All sites	41/101 (40.6%)	22/96 (22.9%)	-17.7% (-32.8 to -2.6)	..	..
All					
Head and neck§	52/93 (55.9%)	22/81 (27.2%)	-28.8% (-45.4 to -12.2)	2.00 (1.28 to 3.12)	0.0003
All sites	74/213 (34.7%)	32/195 (16.4%)	-18.3% (-28.1 to 8.6)	2.15 (1.43 to 3.23)	<0.0001
<b>3 years</b>					
Superficial					
Head and neck	16/26 (61.5%)	9/24 (37.5%)	-24.0% (-56.0 to 7.9)	..	..
All sites	62/93 (66.7%)	29/89 (32.6%)	-34.1% (-50.3 to -17.9)	..	..
Nodular					
Head and neck	30/48 (62.5%)	20/48 (41.7%)	-20.8% (-44.0 to 2.4)	..	..
All sites	41/77 (53.3%)	33/85 (38.8%)	-14.4% (-32.5 to 3.6)	..	..
All					
Head and neck	46/74 (62.2%)	29/72 (40.3%)	-21.9% (-40.7 to -3.1)	1.58 (1.06-2.36)	0.007
All sites	103/170 (60.6%)	62/174 (35.6%)	-25.0% (-37.1 to -12.8)	1.79 (1.36-2.36)	<0.0001

Data are n/N (%), unless otherwise indicated. Analyses adjusted for centre, tumour type, tumour size, tumour site, and immunosuppression. RR=relative risk. \*Surgery-imiquimod. †Imiquimod relative to surgery. ‡From likelihood ratio test. §Primary analysis of interest is head and neck at 6 months.

**Table 4: Cosmetic appearance of lesion (excellent or good) at 6 months and 3 years as rated by two independent dermatologists**

117 patients in the imiquimod group and 109 patients in the surgery group, at 6 months, and in 160 imiquimod treated patients and 166 surgery patients at 3 years; data were missing because patients could not see the lesion sites, and at 6 months for some participants because we changed the scale we used. Participants rated the cosmetic appearance highly (as excellent or good) in both groups at 6 months and 3 years (appendix). Pictures were available for independent review for 213 patients treated with imiquimod and 195 patients treated with surgery at 6 months, and 170 and 174 patients, respectively, at 3 years. Cosmetic appearance at all sites differed significantly between treatment groups in favour of imiquimod, as rated by two independent dermatologists using digital images, at 6 months and 3 years (table 4).

Data for pain during treatment were available for 242 patients treated with imiquimod and 201 patients treated with surgery. 72 (30%) patients in the imiquimod group and 44 (22%) patients in the surgery group had moderate or severe pain at some time during treatment (treatment duration was dependent on treatment and type; table 5); however, 22 (9%) patients treated with imiquimod had moderate or severe pain in the 16 weeks after treatment compared with 41 (20%) of patients who underwent surgery (table 5).

In the safety datasets, 240 (96%) of the 249 patients in the imiquimod group and 202 (88%) of 229 in the surgery group had adverse events (both related and not

	During treatment		Follow-up	
	Imiquimod	Surgery	Imiquimod	Surgery
<b>Superficial</b>				
No pain	44/122 (36%)	35/101 (35%)	63/122 (52%)	25/103 (24%)
Mild or mild to moderate	45/122 (37%)	44/101 (44%)	46/122 (38%)	54/103 (52%)
Moderate, moderate to severe, or severe	33/122 (27%)	22/101 (22%)	13/122 (11%)	24/103 (23%)
<b>Nodular</b>				
No pain	29/120 (24%)	27/100 (27%)	72/111 (65%)	30/103 (29%)
Mild or mild to moderate	52/120 (43%)	51/100 (51%)	30/111 (27%)	56/103 (54%)
Moderate, moderate to severe, or severe	39/120 (33%)	22/100 (22%)	9/111 (8%)	17/103 (17%)
<b>All</b>				
No pain	73/242 (30%)	62/201 (31%)	135/233 (58%)	55/206 (27%)
Mild or mild to moderate	97/242 (40%)	95/201 (47%)	76/233 (33%)	110/206 (53%)
Moderate, moderate to severe, or severe	72/242 (30%)	44/201 (22%)	22/233 (9%)	41/206 (20%)

Pain was recorded in daily diaries, so data were missing for some participants.

**Table 5: Pain during, and 16 weeks after, treatment**

related to treatment) in the first 6 months after start of treatment (table 6). Roughly the same proportions of participants in both groups took drugs to manage the adverse events (table 6). Weeping and itching were common in both groups. Other less common adverse events included occurrence of new tumours, and redness and swelling at tumour site (table 7). In the imiquimod group, 38 (15%) participants needed a dose reduction. 12 (5%) participants in the imiquimod group

	Participants		Events	
	Imiquimod	Surgery	Imiquimod	Surgery
<b>Adverse event in first 6 months after start of treatment</b>				
Superficial	120/128 (94%)	105/114 (92%)	754	521
Nodular	120/126 (95%)	97/115 (84%)	713	380
All	240/254 (94%)	202/229 (88%)	1467	901
<b>ADR in first 6 months after start of treatment</b>				
Superficial	103/128 (80%)	79/114 (69%)	376	234
Nodular	107/126 (85%)	69/115 (60%)	449	187
All	210/254 (83%)	148/229 (65%)	825	421
<b>Adverse event during trial (up to 3 years)</b>				
Superficial	121/128 (95%)	107/114 (94%)	755	525
Nodular	121/126 (96%)	101/115 (88%)	714	388
All	242/254 (95%)	208/229 (91%)	1469	913
<b>ADR during trial (up to 3 years)</b>				
Superficial	104/128 (81%)	79/114 (69%)	377/755 (50%)	234/525 (45%)
Nodular	108/126 (86%)	70/115 (61%)	450/714 (63%)	188/388 (48%)
All	212/254 (83%)	149/229 (65%)	827/1469 (56%)	422/913 (46%)
<b>Serious adverse event*</b>				
Superficial	52/128 (41%)	60/114 (53%)	124/755 (16%)	115/525 (22%)
Nodular	47/126 (37%)	37/115 (32%)	83/714 (12%)	85/388 (22%)
All	99/254 (39%)	97/229 (42%)	207/1469 (14%)	200/913 (22%)
<b>Adverse events of moderate or severe intensity</b>				
Superficial	24/128 (19%)	23/114 (20%)	158/755 (21%)	116/525 (22%)
Nodular	26/126 (21%)	22/115 (19%)	138/714 (19%)	108/388 (28%)
All	50/254 (20%)	45/229 (20%)	296/1469 (20%)	224/913 (25%)
<b>Adverse events for which drugs were taken</b>				
Superficial	88/128 (69%)	76/114 (67%)	249/755 (33%)	216/525 (41%)
Nodular	71/126 (56%)	63/115 (55%)	177/714 (25%)	146/388 (38%)
All	159/254 (63%)	139/229 (61%)	426/1469 (29%)	362/913 (40%)
<b>Adverse events resulting in change in imiquimod dose</b>				
Superficial	15/128 (12%)	..	31	..
Nodular	23/126 (18%)	..	64	..
All	38/254 (15%)	..	95	..

Data are n (%) or n. Proportions for some events have not been provided if we deemed them useless (eg, number of adverse events in the first 6 months compared with those at 3 years, when criteria changed for collection of such events after 1 year). After 1 year from treatment start, we recorded only serious or possible treatment-related events. Five adverse events resulting in withdrawal were treatment related (all in patients in the imiquimod group). Four (2%) in the imiquimod group had wound infections and 12 (5%) in the surgery group. \*No serious adverse events were treatment related. ADR=possibly treatment related adverse event.

**Table 6: Number of participants who had adverse events and number of adverse events (safety dataset)**

withdrew because of adverse events (five [42%] of these events were treatment related, three [25%] were part of treatment failure, and two [17%] were non-related events leading to death as reason for withdrawal). Four (2%) of 229 participants withdrew because of adverse events in the surgery group (all non-related events, three [75%] of which led to death). No deaths or serious adverse events were regarded as related to treatment. 15 (6%) of 249 patients were assessed to have received insufficient imiquimod from compliance diaries, sachet returns, and dose reductions (appendix).

The appendix shows results of the cost-effectiveness analysis.

## Discussion

Our findings show that imiquimod is inferior to surgery for treatment of basal-cell carcinoma because it failed to reach our predefined non-inferiority margin after 3 years of follow-up. Significantly more tumours recurred in patients in the imiquimod group than in those in the surgical group in the time leading up to the first year. We did not record any evidence of patient-rated cosmetic gain for imiquimod that could be traded off against the lower efficacy of imiquimod. However, dermatologist-rated cosmetic outcome was better overall for topical imiquimod. Slightly more participants in the imiquimod group reported pain on treatment than in the surgical group, although direct comparisons were difficult because treatment times differed substantially and pain relief was often given routinely after surgery. More patients had adverse events when treated with the cream than those in the surgery group; however, more patients who underwent surgery had adverse events in the follow-up period. The total costs between treatment methods were not significantly different.

The proportion of patients who had successful treatment with topical imiquimod for superficial basal-cell carcinoma at 1 year in our study is similar to those (87–88%) reported in our Cochrane review,<sup>7</sup> and in a subsequent review that included non-randomised trials, which reported a pooled estimate of 86.2% (95% CI 82–90) for the proportion of patients with a complete response.<sup>9</sup> 83.4% of patients with superficial basal-cell carcinoma treated with topical imiquimod used five times per week responded to treatment as assessed after 12 months in a recent study from the Netherlands, compared with 72.8% of patients treated with photodynamic therapy and 80.1% of patients treated with fluorouracil cream.<sup>19</sup> Findings from another study suggested that thicker lesions (>0.4 mm thickness) might be much more likely to recur than thin lesions.<sup>20</sup>

In our study, where patients were treated with imiquimod daily, more patients with nodular basal-cell carcinoma were successfully treated at 1 year compared with another study that used imiquimod three times a week for either 8 weeks or 12 weeks and reported a successful treatment of 64% of patients,<sup>21</sup> and with a review that suggested a 76% treatment response for nodular tumours.<sup>7</sup> An open-label study of imiquimod (used once daily for 6 weeks) for superficial basal-cell carcinoma reported a 10% cumulative recurrence at 3 years.<sup>22</sup> Another open label study<sup>23</sup> of imiquimod (five times a week for 6 weeks) for superficial basal-cell carcinoma showed a cumulative recurrence of 8.6% at 3 years.

We did not rebiopsy patients with basal-cell carcinoma given topical imiquimod to confirm tumour clearance because this population would not be routinely biopsied if the lesion were regarded as clinically clear. Additionally, further biopsy might induce an inflammatory response that could enhance treatment response. Furthermore, a biopsy scar would have affected the cosmetic result for

	Imiquimod (n=249)	Surgery (n=229)
<b>Patients who had higher frequency mild or moderate adverse events*</b>		
Itching at tumour site	211 (85%)	129 (56%)
Weeping at tumour site	160 (64%)	81 (35%)
New basal-cell carcinoma	64 (26%)	55 (24%)
Erythema or redness at tumour site	56 (22%)	9 (4%)
Cold or flu-type symptoms or feeling of unwell	53 (21%)	21 (9%)
Headache	39 (16%)	38 (17%)
Scab on tumour site	33 (13%)	1 (<1%)
Small spots or pimples close to trial tumour	30 (12%)	5 (2%)
Soreness of tumour site	24 (10%)	16 (7%)
Bleeding at tumour site	21 (8%)	8 (3%)
Pain at tumour site	12 (5%)	17 (7%)
Swelling at tumour site	10 (4%)	19 (8%)
<b>Patients who had higher frequency severe, life-threatening, or disabling events†</b>		
Cold or flu-type symptoms	7 (3%)	0
Inflammatory reaction to treatment	4 (2%)	0
Heart attack or heart failure	3 (1%)	4 (2%)
Pneumonia	1 (<1%)	4 (2%)

Data are n (%), unless otherwise indicated. \* >5% in either group. † >1% in either group

**Table 7: Number of participants who had higher frequency mild or moderate or severe, life-threatening, or disabling adverse events of all types (safety dataset)**

imiquimod, which was an important outcome to measure in this study.

Few studies have compared the cost-effectiveness of surgical treatment versus topical imiquimod for superficial basal-cell carcinoma. One study<sup>24</sup> estimated the mean cost per patient given imiquimod 5% cream to be lower than that of a patient assigned surgery for a superficial basal-cell carcinoma (621 vs 676 euros), but costs associated with treatment of initial treatment failures or recurrences were not addressed. Another study<sup>25</sup> compared the cost of imiquimod with surgery and reported imiquimod to be more cost effective in the short term but more expensive in the long term. One study<sup>26</sup> compared the cost-effectiveness of imiquimod with that of a range of other treatments and showed the cost of imiquimod to be higher. Future studies might compare other treatments used for low-risk basal-cell carcinomas, such as electrodesiccation and curettage, with topical imiquimod or photodynamic therapy.

To our knowledge this study is the first large, independent, pragmatic study comparing imiquimod with surgery in a wide range of patients who might typically be considered for such treatment in primary care (panel). Selection bias was unlikely due to strong concealment of the allocation sequence, and the modified intention-to-treat analysis shows similar results to our per-protocol analysis. There were few missing data for the risk factors we adjusted for, so this

### Panel: Research in context

#### Systematic review

We did a Cochrane systematic review of interventions for basal-cell carcinoma when planning our study in 2002, which we then updated in 2007.<sup>7</sup> In the Cochrane review we searched six databases and contacted companies and identified 27 randomised controlled trials of mainly poor quality as judged by method of randomisation, allocation concealment, blinding, and whether an intention-to-treat analysis and unit of analysis issues were considered. The largest study included 347 patients. Nine short-term studies combined using a random-effects model suggested a success rate of 87% for imiquimod in the treatment of superficial basal-cell carcinoma with a once-daily regimen for 6 weeks, and a 76% treatment response with treatment of nodular basal-cell carcinoma for 12 weeks, when measured histologically. We then searched PubMed and CENTRAL from January, 2006, to June, 2013, with the same terms as used in our Cochrane review, to identify new relevant studies of interventions for basal-cell carcinoma. None of the newly identified studies directly compared topical imiquimod with excisional surgery.

#### Interpretation

To our knowledge this study is the first large, independent, pragmatic study comparing imiquimod with surgery in patients who might typically be considered for such treatment in primary care. Our findings show that topical imiquimod is inferior to surgery with no clear cosmetic or cost benefits. Success rates for excisional surgery were high. The study provides a useful estimate of response rates for topical imiquimod in clinical practice for both low-risk superficial and nodular basal-cell carcinoma at 3 years. Topical imiquimod might still be a useful treatment option for people with low-risk basal-cell carcinomas who have more than one superficial basal-cell carcinoma, those treated in primary care where success rates for excisional surgery can be considerably lower than in secondary care, and for those who prefer to use a cream at home, especially since recurrences are usually easy to identify and deal with surgically. Other treatments for low-risk and multiple basal-cell carcinomas include photodynamic therapy, electrodesiccation and curettage, topical fluorouracil, and cryotherapy. However, none of these treatments have been assessed long term, except for photodynamic therapy,<sup>27</sup> which has shown similar long-term response rates to those reported for imiquimod in this study.

issue had little effect on the number of participants on which our regression models were based. Study limitations include the fact that we used imiquimod 7 days a week, rather than the presently licensed 5 days a week. Increased participant support in the use of imiquimod and dealing with side-effects might have improved results in the imiquimod group. Additionally, some of the surgeons were trained in advanced surgery



and were therefore not typical primary-care or secondary-care professionals, which means that the surgical results in this study might have been better than what would be observed in general practice. Comparisons of pain on treatment were difficult because the time for which patients used imiquimod was much longer than the 1 day in which patients underwent for surgery. Absence of a masked clinical assessment at 3 years might have favoured surgery because it was done by those who traditionally undertake surgery. We also lost some precision in our estimates of treatment effects by revising our sample size from 740 to 500 for pragmatic reasons.

In terms of external validity, the study could have favoured slightly younger people with basal-cell carcinoma who were more mobile than some of the older and more frail patients who declined to participate; furthermore, individuals entering the study were motivated about the prospect of use of topical imiquimod, which was not licensed for basal-cell carcinoma at the start of the study.

Although our study showed imiquimod to be inferior to surgery according to our predefined non-inferiority margin, others might consider the overall success rate at 3 years still clinically useful, especially because low-risk recurrences of basal-cell carcinoma can be treated. In other words, some policy makers might consider use of topical imiquimod as part of a sequential treatment approach that treats most people with low-risk lesions successfully at home and those who fail with surgery. Use of imiquimod cream for low-risk basal-cell carcinoma might be a matter of patient choice guided by convenience and acceptability of the intervention, although it should be pointed out that surgery is more effective and leads to similar patient-adjudicated cosmetic outcomes as does imiquimod cream. The difference between surgery and imiquimod cream might be less in primary care than reported in this study because family doctors perform surgery less successfully (complete excision in 32–78% of patients) than dermatologists (72–92%).<sup>28–31</sup> A stronger case can be made for treatment of superficial basal-cell carcinoma at low-risk sites to be managed in primary care with imiquimod than for low-risk nodular tumours. Such patients would need to be followed up long-term in view of the lower success of imiquimod compared with surgery. Excisional surgery remains the best treatment for low-risk basal-cell carcinoma, but other factors, such as patient choice, size and site of the lesion, and whether the patient has more than one lesion, might allow alternative treatments such as imiquimod cream, fluorouracil cream, and photodynamic therapy to be considered.<sup>19,27</sup>

#### Contributors

FB-H wrote the outline proposal and the main protocol, was on the trial management group, wrote the first draft of the paper, and is the grant holder. MO was the study coordinator and was on the trial management

group; updated the protocol as necessary; obtained ethics amendment approvals; supervised the study nurses; designed the data capture forms; wrote instruction documents as needed; built and maintained the database; ensured data quality, including double data entry and 100% checks; prepared datasets for analysis, interpretation, and tabulation of the results, and contributed to writing of the final report. SA was the trial statistician and a member of the trial management group, participated in the design of the study, commented on revisions of the protocol, wrote the study analysis plan, did the statistical analysis, and contributed to the drafting of this manuscript and the interpretation of the results. HW contributed to the funding proposal, the main protocol, was chief investigator, and contributed to trial delivery, interpretation of the results, and writing of the final report; WP recruited patients, was on the trial management group, and contributed to interpretation of results and approval of the final report; GC recruited patients, was on the trial management group, and contributed to interpretation of results and approval of the final report. PM contributed to the funding proposal and the main protocol, was study health economist, designed and implemented the cost-effectiveness analyses, and contributed to the drafting of this manuscript.

#### Conflicts of interest

We declare that we have no conflicts of interest.

#### Acknowledgments

The study was financed by Cancer Research UK. We thank the patients who agreed to participate in this study and all those who helped with running the study; MEDA for donating 5% imiquimod cream free of charge; John English for helping with the masked assessment of cosmetic appearance; and Jack Tweed (patient–public member) for his suggestions on initial study design.

#### References

- Wong C, Strange R, Lear J. Basal cell carcinoma. *BMJ* 2003; **327**: 794–98.
- Lomas A. A systematic review of worldwide incidence of non-melanoma skin cancer. *Br J Dermatol* 2012; **166**: 1069–80.
- Bath-Hextall F, Leonardi-Bee J, Smith C, Meal A, Hubbard R. Trends in incidence of basal cell carcinoma; additional evidence from a UK-primary care database study. *Int J Cancer* 2007; **121**: 2105–08.
- Skellett A, Hafiji J, Greenberg D, Wright K, Levell N. The incidence of basal cell carcinoma in the under-30s in the UK. *Clin Exp Dermatol* 2012; **37**: 227–29.
- Morris S, Cox B, Bosanquet N. Cost of skin cancer in England. *Eur J Health Econ* 2009; **10**: 267–73.
- Chen S, Bravata D, Weil E, Olkin I. A comparison of dermatologists' and primary care physicians' accuracy in diagnosing melanoma. *Arch Dermatol* 2001; **137**: 1627–34.
- Bath-Hextall F, Perkins W, Bong J, Williams H. Interventions for basal cell carcinoma of the skin. *Cochrane Database Syst Rev* 2007; **1**: CD003412.
- National Collaborating Centre for Cancer. Improving outcomes for people with skin tumours including melanoma (update): the management of low-risk basal-cell carcinomas in the community. May, 2010. <http://www.nice.org.uk/nicemedia/live/10901/48878/48878.pdf> (accessed Oct 22, 2013).
- Roozeboom M, Artis A, Nelemans P, Kelleners-Smeets N. Overall treatment success after treatment of primary superficial basal cell carcinoma: a systematic review and meta-analysis of randomized and nonrandomized trials. *Br J Dermatol* 2012; **167**: 733–56.
- Electronic Medicines Compendium (eMC). Aldara 5% cream. June 24, 2010. <http://www.medicines.org.uk/emc/medicine/8/spc#INDICATIONS> (accessed Dec 23, 2013).
- Schön M, Schön MP. The antitumoral mode of action of imiquimod and other imidazoquinolines. *Curr Med Chem* 2007; **14**: 681–87.
- Micali G, Lacarrubba F, Dinotta F, Massimino D, Nascia MR. Treating skin cancer with topical cream. *Expert Opin Pharmacother* 2010; **11**: 1515–27.
- Ozolins M, Williams HC, Armstrong SJ, Bath-Hextall FJ. The SINS trial: a randomised controlled trial of excisional surgery versus imiquimod 5% cream for nodular and superficial basal cell carcinoma. *Trials* 2010; **11**: 42.

- 14 Baxter JM, Patel AN, Varma S. Facial basal cell carcinoma. *BMJ* 2012; **21**: 345.
- 15 Marks R, Gebauer K, Shumack S, et al. Imiquimod 5% cream in the treatment of superficial basal cell carcinoma: results of a multicentre 6-week dose-response trial. *J Am Acad Dermatol* 2001; **44**: 807–13.
- 16 Rowe DE, Carroll RJ, Day CL Jr. Long-term recurrence rates in previously untreated (primary) basal cell carcinoma: implications for patient follow-up. *J Dermatol Surg Oncol* 1989; **15**: 315–328.
- 17 Assman S, Pocock S, Enos L, Kasten L. Subgroup analysis and other (mis)uses of baseline data in clinical trials. *Lancet* 2000; **355**: 1064–69.
- 18 Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004; **159**: 702–06.
- 19 Arits AH, Mosterd K, Essers BA, et al. Photodynamic therapy versus topical imiquimod versus topical fluorouracil for treatment of superficial basal-cell carcinoma: a single blind, non-inferiority, randomised controlled trial. *Lancet Oncol* 2013; **14**: 647–54.
- 20 McKay KM, Sambrano BL, Fox PS, Bassett RL, Chon S, Prieto VG. Thickness of superficial basal cell carcinoma predicts imiquimod efficacy, a proposal for thickness-based definition of superficial basal cell carcinoma. *Br J Dermatol* 2013; **169**: 549–54.
- 21 Eigentler T, Kamin A, Weide B, et al. A phase III, randomized, open label study to evaluate the safety and efficacy of imiquimod 5% cream applied thrice weekly for 8 and 12 weeks in the treatment of low-risk nodular basal cell carcinoma. *J Am Acad Dermatol* 2007; **57**: 616–21.
- 22 Quirk C, Gebauer K, De'Ambrosio B, Slade H, Meng T. Sustained clearance of superficial basal cell carcinoma treated with imiquimod cream 5%: results of a prospective 5-year study. *Cutis* 2010; **85**: 318–24.
- 23 Gollnick H, Barona C, Frank R. Recurrence rate of superficial basal cell carcinoma following treatment with imiquimod 5% cream: conclusion of a 5-year long-term follow-up study in Europe. *Eur J Dermatol* 2008; **18**: 677–82.
- 24 Vanaclocha F, Dauden E, Badia X. Cost-effectiveness of treatment of superficial basal cell carcinoma: surgical excision vs. imiquimod 5% cream. *Br J Dermatol* 2007; **156**: 769–71.
- 25 De Cock M, Nuijten J, Hollestein A, Hamel-Gariepy L. Cost-effectiveness model of Aldara (imiquimod) cream 5% in superficial basal cell carcinoma in the Netherlands. *Value Health* 2005; **8**: A144.
- 26 Sverre J, Kristensen F, Hamel-Gariepy L, Albrektsen T. Cost-effectiveness analysis: Aldara (imiquimod) cream 5% in the treatment of superficial basal cell carcinoma in Norway. *Value Health* 2005; **8**: A143.
- 27 Rhodes L, de Rie M, Leifsdottir R, et al. Five-year follow-up of a randomized, prospective trial of topical methyl aminolevulinate photodynamic therapy vs surgery for nodular basal cell carcinoma. *Arch Dermatol* 2007; **143**: 1131–36.
- 28 British Society for Dermatological Surgery. Incomplete excision rates of basal cell carcinomas in primary care and dermatology: a multicentre audit. Liverpool, UK: British Association of Dermatologists, 2008.
- 29 British Society for Dermatological Surgery. Dermatological surgery: a comparison of activity and outcomes in primary and secondary care. Liverpool, UK: British Association of Dermatologists, 2008.
- 30 Dabrera G. Is the adequacy of excision of basal cell carcinoma related to operator experience? *Clin Exp Dermatol* 2007; **32**: 103–04.
- 31 Murchie P, Delaney E, Thompson W, Lee A. Excising basal cell carcinomas: comparing the performance of general practitioners, hospital skin specialists and other hospital specialists. *Clin Exp Dermatol* 2008; **33**: 565–71.